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CLAIMS

- 1. An agent for expression of long-term potentiation of synaptic transmission, which comprises a compound having a brain somatostatin activation property as an active ingredient.
 - 2. The agent for expression of long-term potentiation of synaptic transmission of claim 1, wherein the compound exerts an action to promote a release of brain somatostatin through suppression of a negative feedback mechanism of brain somatostatin release.
 - 3. The agent for expression of long-term potentiation of synaptic transmission of claim 1 or claim 2, wherein the compound has the following formula [I]:

 R^1 —A—N N—N—Y— R^3 [I]

wherein

wherein

is lower alkyl, aryl, ar(lower)alkoxy or heterocyclic group, each of which may be substituted with halogen,

20 R² is hydrogen atom or lower alkyl,

R³ is cyclo(lower) alkyl, arylor ar(lower) alkyl, each of which may be substituted with halogen,

A is $-CO_-$, $-SO_2_-$ or lower alkylene, and

Y is $-CO_{-}$, $-SO_{2}$ or $-CONH_{-}$,

- 25 or pharmaceutically acceptable salts thereof.
 - 4. The agent for expression of long-term potentiation of synaptic transmission of claim 1 or claim 2, wherein the compound has the following formula [II-1]:

Sp/

R⁴ is acyl,

is lower alkyl, lower alkoxy, lower alkylamino, lower

alkenyl, lower alkenyloxy, lower alkenylamino, lower

alkynyl, lower alkynyloxy, lower alkynylamino,

cyclo(lower)alkyl, cyclo(lower)alkyloxy,

cyclo(lower)alkylamino, aryl, aryloxy, arylamino,

a heterocyclic group or amino substituted with

a heterocyclic group, each of which may be substituted with suitable substituent(s); or acyl; is a\single bond, -CO- or -SO₂-,

z is a\single bond, -CO- or -SO₂-,
E is lower alkylene optionally substituted with suitable
substituent(s),

X is CH or N,

J is a single bond, lower alkylene or

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an N-protective group, aryl, acyl or a heterocyclic group, is -CH₂-, -CO-, -SO₂- or -N=CH-, and are each hydrogen or lower alkyl, or are taken together to form lower alkylene optionally condensed with a cyclic hydrocarbon or a heterocyclic ring,

wherein R⁸ is hydrogen, lower alkyl, substituted-lower alkyl,

provided that when X is N,

then 1) J is a single bond, and Q is $-CH_2-$, -CO- or $-SO_2-$, or

2) J is lower alkylene,
or pharmaceutically acceptable salts thereof.

5. The agent for expression of long-term potentiation of synaptic transmission of claim 1 or claim 2, wherein the compound has the following formula [II-2]:

 R^4-N $X-J-Q-R^7$ II-2

wherein

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R4 is acyl,

R⁷ is aryl, aryloxy or arylamino, the aryl moiety of all of which may be substituted with halogen; pyridyl; or pyridylamino;

5 X is Ch or N,

J is a single bond, lower alkylene or

R⁸ --N--

wherein R^8 is hydrogen, lower alkyl or an N-protective group, is $-CH_2-$, -CO- or $-SO_2-$,

provided that when X is N, then J is a single bond or lower alkylene, or pharmaceutically acceptable salts thereof.

- 6. The agent for expression of long-term potentiation of synaptic transmission of any of claim 1 to claim 5, which is an agent for the prophylaxis or treatment of gerebral diseases.
- 7. The agent for expression of long-term potentiation of synaptic transmission of claim 6, which is an agent for the prophylaxis or treatment 20 of dementia or amnesia.
 - 8. A method for expressing long-term potentiation of synaptic transmission, comprising administering an effective amount of a compound having a brain somatostatin activation property.
 - 9. The method for expressing long-term potentiation of synaptic transmission of claim 8, wherein the compound exerts an action to promote a release of brain somatostatin through suppression of a negative feedback mechanism of brain somatostatin release.
 - 10. The method for expressing long-term potentiation of synaptic transmission of claim 8 or claim 9, wherein the compound has the following formula [I]:

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$$R^1-A-N$$
 $N-N-Y-R^3$ [1]

wherein

is lower alkyl, aryl, ar(lower)alkoxy or heterocyclic group, each of which may be substituted with halogen,

R² is hydrogen atom or lower alkyl,

R³ is cyclo(lower)alkyl, arylorar(lower)alkyl, each of which may be substituted with halogen,

A is -CO-, -SO₂- or lower alkylene, and

10 Y is -CO-, -SO₂- or -CONH-,

or pharmaceutically acceptable salts thereof.

11. The method for expressing long-term potentiation of synaptic transmission of claim 8 or claim 9, wherein the compound has the following formula [II-1]:

$$R^4$$
— Z — N
 K
 X — J — Q — R^7 [II-1]

wherein

 R^4 is acyl, 20 R^7 is lower alkyl, lower alkoxy, lower alkylamino, lower alkenyl, lower alkenyloxy, lower alkenylamino, lower alkynyl, lower alkynyloxy, lower alkynylamino, cyclo(lower)alkyl, cyclo(lower)alkyloxy, cyclo(lower)alkylamino, aryl, aryloxy, arylamino, 25 a heterocyclic group or amino substituted with a heterocyclic group, each of which may be substituted with suitable substituent(s); or acyl; Z is a single bond, -co- or $-so_2-$, E is lower alkylene optionally substituted with suitable 30 substituent(s), is CH or N, X J is a single bond, lower alkylene or



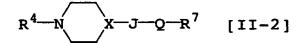
wherein R^θ is hydrogen, lower alkyl, substituted-lower alkyl, an N-protective group, aryl, acyl or a heterocyclic group,

5 Q is $-CH_2-$, -CO-, $-SO_2-$ or -N=CH-, and

R⁵ and R⁶ are each hydrogen or lower alkyl, or are taken together to form lower alkylene optionally condensed with a cyclic hydrocarbon or a heterocyclic ring,

provided that when X is N,

- 10 then 1) J is a single bond, and Q is -CH₂-, -CO- or -SO₂-, or
 2) J is lower alkylene,
 or pharmaceutically acceptable salts thereof.
- 12. The method for expressing long-term potentiation of synaptic transmission of claim 8 or claim 9, wherein the compound has the following formula [II-2]:



wherein

20 R4 is acyl,

R⁷
is aryl, aryloxy or arylamino, the aryl moiety of all of which may be substituted with halogen; pyridyl; or pyridylamino;

X is CH or N,

25 J is a single bond, lower alkylene or



- wherein R^{θ} is hydrogen, lower alkyl or an N-protective group, is $-CH_2-$, -CO- or $-SO_2-$,
- 30 provided that when X is N, then J is a single bond or lower alkylene,

or pharmaceutically acceptable salts thereof.

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- 13. The method for expressing long-term potentiation of synaptic transmission of any of claim 8 to claim 12, which is a method for the prophylaxis or treatment of cerebral diseases.
- 14. The method for expressing long-term potentiation of synaptic transmission of claim 13, which is a method for the prophylaxis and/or treatment of dementia or amnesia.

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- 15. Use of a compound having a brain somatostatin activation property for the production of an agent for the expression of long-term potentiation of synar ransmission.
- 16. The use of a compou ing a brain somatostatin activation property according to claim 15, wherein the compound exerts an action to promote a release of brain somatostatin through suppression of a negative feedback mechanism of brain somatostatin release.
- 20 17. The use of a compound having a brain somatostatin activation property according to claim 15 or claim 16, wherein the compound has the following formula [I]:

$$R^1-A-N$$
 R^2
 $N-Y-R^3$ [I]

25 wherein

R¹ is lower alkyl, aryl ar(lower)alkoxy or heterocyclic group, each of which may be substituted with halogen,

R² is hydrogen atom or ldwer alkyl,

R³ is cyclo(lower)alkyl, arvlorar(lower)alkyl, each of which may be substituted with halogen,

A is $-CO_-$, $-SO_2_-$ or lower alkylene, and

Y is $-CO_{-}$, $-SO_{2}$ or $-CONH_{-}$

or pharmaceutically acceptable salts thereof.

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18. The use of a compound having a brain somatostatin activation property according to claim 15 or claim 16, wherein the compound has the following formula \[II-1]:

$$R^4-Z-N$$
 $X-J-Q-R^7$ [II-1]
 R^5
 R^6

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wherein

R4

is acyl,

 \mathbb{R}^7

is lower alkyl, lower alkoxy, lower alkylamino, lower alkeny∜, lower alkenyloxy, lower alkenylamino, lower

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alkynyl lower alkynyloxy, lower alkynylamino,

cyclo(lover)alkyl, cyclo(lower)alkyloxy,

cyclo(lower)alkylamino, aryl, aryloxy, arylamino,

a heterocyclic group or amino substituted with a heterocyclic group, each of which may be substituted with

is a single bond, -CO- or -SO₂-, Z

is lower alky hene optionally substituted with suitable Е

substituent(s),

is CH or N, X

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is a single bond \ lower alkylene or

suitable substituent(s); or acyl;



wherein R⁸ is hydrogen, lower alkyl, substituted-lower alkyl, an N-protective group, aryl, acyl or a heterocyclic group, is $-CH_2-$, -CO-, $-SO_2-$ of -N=CH-, and

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R⁵ and R⁶ are each hydrogen or lower alkyl, or are taken together to form lower alkylene optionally condensed with a cyclic

hydrocarbon or a heterocydlic ring,

provided that when X is N,

then 1) J is a single bond, and Q is $-CH_2-$, -CO- or -SO₂-, or 30

2) J is lower alkylene,

or pharmaceutically acceptable salts thereof.

19. The use of a compound having a brain somatostatin activation property according to claim 15 or claim 16, wherein the compound has the following formula \[II-2]:

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wherein

R4

is acyl,

 R^7

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is arxl, aryloxy or arylamino, the aryl moiety of all of which hay be substituted with halogen; pyridyl; or pyridylamino;

X

is CH or W,

J

is a single bond, lower alkylene or

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wherein R⁸ is hydrogen, lower alkyl or an N-protective group, is $-CH_2-$, -CO- or $-CO_2-$,

provided that when X is N, then λ is a single bond or lower alkylene, or pharmaceutically acceptable alts thereof.

- 20. The use of a compound having a brain somatostatin activation property according to any of claim 15 to claim 19, which is for the production of an agent for the prophylaxis and/or Areatment of cerebral diseases.
- 25 21. The use of a compound having a brain somatostatin activation property according to claim 20, which is for the production of an agent for the prophylaxis and/or treatment of dementia or amnesia.
- 22. A pharmaceutical composition for expression of long-term potentiation of synaptic transmission, which comprises a compound 30 having a brain somatostatin activation property, and a pharmaceutically acceptable carrier or excipient.



23. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of claim 22, wherein the compound exerts an action to promote a release of brain somatostatin through suppression of a negative feedback mechanism of brain somatostatin release.

24. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of claim 22 or claim 23, wherein the compound has the following formula [I]:

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$$R^1-A-N$$
 $N-N-Y-R^3$ [I]

wherein

Y

is lower alkyl, aryl, ar(lower)alkoxy or heterocyclic group, each of which may be substituted with halogen,

15 R² is hydrogen atom or lower alkyl,

R³ is cyclo(lower)alkyl, arylorar(lower)alkyl, each of which may be substituted with halogen,

A is -CO-, -SO₂- or lower alkylene, and

20 or pharmaceutically acceptable salts thereof.

is $-CO_-$, $-SO_2$ - or $-CONH_-$,

25. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of claim 22 or claim 23, wherein the compound has the following formula [II-1]:

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$$R^4-Z-N$$
 $X-J-Q-R^7$ [II-1]

wherein

R⁴ is acyl,

30 R⁷ is lower alkyl, lower alkoxy, lower alkylamino, lower alkenyl, lower alkenyloxy, lower alkenylamino, lower alkynyl, lower alkynyloxy, lower alkynylamino,

cyclo(lower)alkyl, cyclo(lower)alkyloxy, cyclo(lower)alkylamino, aryl, aryloxy, arylamino, a heterocyclic group or amino substituted with a heterocyclic group, each of which may be substituted with 5 suitable substituent(s); or acyl; Z is a single bond, -CO- or $-SO_2-$, is lower alkylene optionally substituted with suitable E substituent(s), is CH or N, X 10 J is a single bond, lower alkylene or

wherein R⁸ is hydrogen, lower alkyl, substituted-lower alkyl, an N-protective group, aryl, acyl or a heterocyclic group, is -CH₂-, -CO-, -SO₂- or -N=CH-, and R⁵ and R⁶ are each hydrogen or lower alkyl, or are taken together to form lower alkylene optionally condensed with a cyclic hydrocarbon or a heterocyclic ring,

20 then 1) J is a single bond, and Q is -CH₂-, -CO- or -SO₂-, or
2) J is lower alkylene,
or pharmaceutically acceptable salts thereof.

26. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of claim 22 or claim 23, wherein

$$R^4$$
— N X — J — Q — R^7 [II-2]

the compound has the following formula [II-2]:

wherein

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30 R⁴ is acyl,

provided that when X is N,

R⁷ is aryl, aryloxy or arylamino, the aryl moiety of all of which may be substituted with halogen; pyridyl; or pyridylamino; x is CH or N,

j is a single bond, lower alkylene or

R⁸

5 wherein R^8 is hydrogen, lower alkylor an N-protective group, Q is $-CH_2-$, -CO- or $-SO_2-$,

provided that when X is N, then J is a single bond or lower alkylene, or pharmaceutically acceptable salts thereof.

- 27. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of any of claim 22 to claim 26, which is a pharmaceutical composition for the prophylaxis or treatment of cerebral diseases.
- 15 28. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of claim 27, which is a pharmaceutical composition for the prophylaxis or treatment of dementia or amnesia.
- 20 29. A method for screening an agent for expression of long-term potentiation of synaptic transmission, which comprises using a somatostatin releasing action as an index.
- 30. The screening method of claim 29, which is a screening method of 25 an anti-dementia agent or anti-amnesia agent.
 - 31. A method for screening an agent for expression of long-term potentiation of synaptic transmission, which comprises stimulating hippocampal slices, bringing a hippocampal slice into contact with a test compound, measuring an amount of somatostatin released from the hippocampal slice and/or a release time thereof, measuring an amount of somatostatin released from a hippocampal slice and/or a release time thereof in the absence of a contact with the test compound, and comparing the amounts and/or the times to calculate the amount of somatostatin released from the hippocampal slice and/or the release



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time thereof caused by the contact with the test compound.

32. The screening method according to claim 31, which is a screening method of an anti-dementia agent or anti-amnesia agent.

33. The agent for expression of long-term potentiation of synaptic transmission of claim 1, wherein the compound having the brain somatostatin activation property is a compound obtained by the screening method of any of claim 29 to claim 32.

34. The method for expressing long-term potentiation of synaptic transmission according to claim 8, wherein the compound having the brain somatostatin activation property is a compound obtained by the screening method of any of claim 29 to claim 32.

35. The use of a compound having a brain somatostatin activation property according to claim 15, where the compound having the brain somatostatin activation property is obtained by the screening method of any of claim 29 to claim 32.

36. The pharmaceutical composition for expression of long-term potentiation of synaptic transmission of claim 22, wherein the compound having the brain somatostatin activation property is a compound obtained by the screening method of any of claim 29 to claim 32.

37. A commercial package comprising the pharmaceutical composition for expression of long-term potentiation of synaptic transmission of any of claim 22 to claim 28 or claim 36 and a written matter associated therewith, wherein the written matter states that the pharmaceutical composition can or should be used for expression of long-term potentiation of synaptic transmission.

38. A compound selected by the screening method described in any of claim 29 to claim 32.

